CHRONIC TOXICITY SUMMARY

METHYLENE DIPHENYL ISOCYANATE

(diphenylmethane diisocyanate)

CAS Registry Number: 101-68-8

I. Chronic Reference Exposure Level

Inhalation reference exposure level	**0.7 µg/m^3**
Critical effect(s)	Hyperplasia of the olfactory epithelium in rats
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Light yellow solid
Molecular formula	$C_{15}H_{10}N_2O_2$ (monomer)
Molecular weight	Variable (monomer = 250.27 g/mol)
Density	1.197 g/cm^3 @ 70°C (monomer)
Boiling point	196°C (monomer)
Melting point	37°C (monomer)
Vapor pressure	0.001 torr @ 40°C (monomer)
Solubility	Soluble in acetone, benzene, kerosene, and nitrobenzene (monomer)
Conversion factor	Monomer: 1 ppm = 10.2 mg/m^3 at 25°C; Not applicable for polymer

III. Major Uses or Sources

Methylene diphenyl isocyanate (MDI) is used for bonding rubber to nylon. MDI is also used in the manufacture of lacquer coatings and in the production of polyurethane resins and spandex fibers (HSDB, 1995). It is often handled in a partially polymerized form ("MDI polymer"), which has a much lower vapor pressure than the monomer. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 30,398 pounds of MDI (CARB, 2000).

IV. Effects of Human Exposure

A 5-year occupational study of 107 workers from a polyurethane plastic manufacturing plant examined pulmonary function, respiratory symptoms, and smoking habits (Musk *et al.*, 1982, 1985). No significant changes in pulmonary function or respiratory symptoms were observed

when controlled for smoking. Mean MDI concentrations measured ranged from 0.0003 to 0.0006 ppm.

Significantly increased prevalence of asthma in female workers and of chronic bronchitis in male and female workers was observed following occupational exposure to low levels of MDI (<0.02 ppm) (Pham *et al.*, 1988). Workers from two plants were grouped by job classification and evaluated in this study conducted in 1976; workers were grouped as unexposed (62 men, 21 women), indirectly exposed (61 men, 56 women), or directly exposed (91 men, 27 women). Further characterization of the exposure groups was not presented. Decrements in pulmonary function (measured by VC, FEV_1 and single-breath carbon monoxide diffusion tests) were observed in men in the direct and indirect exposure groups: decrements in men with a history of direct exposure to MDI were statistically significant. Workers were also grouped by duration of occupational exposure (<20 months, 20-60 months, >60 months). Workers with known (direct or indirect) occupational exposure to MDI for greater than 60 months exhibited statistically significant decrements in pulmonary function tests. The follow-up examination of this study describes data from male workers only. At the time of the 5-year follow-up, air levels had been reduced to below the maximum allowed air concentration of 0.005 ppm by a modification of the ventilation system. Statistically significant decrements in pulmonary function were observed again in workers with known direct occupational exposure to MDI. Workers who were exposed at the time of the 1976 study but had since been removed from exposure did not exhibit decrements in pulmonary function, leading the authors to conclude that the effects of low-level exposure to MDI are to some extent reversible. Flaws in study design, including lack of exposure characterization, attrition, and inclusion of asthmatics in cohorts, preclude a quantitative assessment of MDI exposure on lung function.

An epidemiologic study of foundry workers reported more respiratory symptoms and significantly lower mean FEV_1 and maximum mid-expiratory flow at 25-75% in exposed workers compared to controls (Johnson *et al.*, 1985). However, MDI-exposed workers also had unquantified exposure to silica, metal dust, phenol formaldehyde, and a pyridine derivative precluding the evaluation of respiratory effects resulting from MDI exposure.

A worker with 5 years occupational exposure and suspected MDI hypersensitivity was exposed continuously in a controlled chamber to 5 ppb for 15 minutes, then 10 ppb for 30 minutes, and 20 ppb for 15 minutes (Marczynski *et al.*, 1992). The worker had not been exposed to MDI in the workplace for 5 days prior to the test challenge. Exposure to MDI resulted in an immediate, moderate, asthmatic reaction associated with significant hypoxemia.

IgG antibodies recognizing MDI-human serum albumin conjugates were detected in 4 of 5 MDI-exposed workers (Aul *et al*., 1999). The levels of specific IgG antibodies were more elevated with polymeric MDI compared with monomeric MDI.

A workplace death of a 39-year-old foundry worker was ascribed to occupational asthma induced by MDI exposure (Carnio *et al*., 1997). Postmortem pulmonary findings included epithelial desquamation, mucosal eosinophilic/neutrophilic infiltration, bronchial vessel dilatation, and edema and hypertrophy of smooth muscle.

V. Effects of Animal Exposure

Rats were exposed to 0.2, 1.0, and 6.0 mg/m^3 aerosolized MDI polymer 6 hours per day, 5 days per week for 24 months (Reuzel *et al.*, 1990; 1994). Statistically significant increased incidences of basal cell hyperplasia, olfactory epithelial degeneration, alveolar duct epithelialization, localized alveolar bronchiolization, and adenomas were observed in male and female rats exposed to 6.0 mg/m^3 MDI. An accumulation of macrophages with yellow pigment was also noted in the lungs and mediastinal lymph nodes. Male rats exposed to this concentration also exhibited a statistically significant increase in the incidence of Bowman's gland hyperplasia. Male rats exposed to 1 mg/m^3 MDI also exhibited statistically significant increased incidences of basal cell hyperplasia and Bowman's gland hyperplasia. An accumulation of macrophages with yellow pigment was observed in the lungs of female rats and the lungs and mediastinal lymph nodes of male rats exposed to 1 mg/m^3. No adverse effects were noted in rats exposed to 0.2 mg/m^3 MDI.

Hyperplasia of the olfactory epithelium with MDI exposure (Reuzel *et al.*, 1990; 1994)

Concentration (mg/m^3)	*Males*			*Females*			*Combined*		
	Responders	*N*	*Incidence*	*Responders*	*N*	*Incidence*	*Responders*	*N*	*Incidence*
0	14	60	0.23	4	60	0.067	18	120	0.15
0.2	13	60	0.22	8	60	0.13	21	120	0.18
1	26	60	0.43	8	60	0.13	34	120	0.28
6	32	60	0.53	49	59	0.83	81	119	0.68

Guinea pigs were exposed to 2 ppm MDI 3 hours per day for 5 days (Aizicovici *et al.*, 1990). Qualitative immunostaining techniques indicated that MDI was localized in the respiratory tract. The spleen, lymph nodes, and thymus had very little staining. However, another study exposed guinea pigs to 4 ppb radiolabelled toluene diisocyanate (TDI) for 1-hour and found measurable radioactivity in extrathoracic tissues and body fluids (Kennedy *et al.*, 1989). Therefore, there is a possibility that MDI may be transported to sites other than the respiratory tract, such as the ovaries and testes, following inhalation exposure.

Gravid Wistar rats, Crl:(WI)BR, were exposed by whole-body inhalation to clean air (control) and to 1, 3, and 9 mg/m^3 MDI, respectively, for 6 hr per day from days 6 to 15 post conception (Buschmann *et al.*, 1996). Rats were killed on day 20. The lung weights in the high-dose group were significantly increased compared to the sham-treated control animals. Treatment did not influence any other maternal and/or fetal parameters investigated (including maternal weight gain, number of corpora lutea, implantation sites, pre-and postimplantation loss, fetal and placental weights, gross and visceral anomalies, and degree of ossification). A slight but significant increase in litters with fetuses displaying asymmetric sternebra(e) was observed after

treatment with the highest dose. Although the relevance of an increase of this minor anomaly in doses which maternal toxicity is limited and within the limits of biological variability, a substance-induced effect in the high-dose group cannot be excluded with certainty. Thus, the authors reported a NOAEL of 3 mg/m^3 for embryotoxic effects.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Reuzel *et al.*, 1990; 1994
Study population	Rats
Exposure method	Inhalation of polymeric aerosolized MDI (0, 0.2, 1.0, and 6.0 mg/m^3)
Critical effects	Hyperplasia of the olfactory epithelium
LOAEL	1 mg/m^3
NOAEL	0.2 mg/m^3
Benchmark Concentration (BMC_{05})	0.25 mg/m^3 (95% lower confidence limit on concentration for a 5% incidence of response based on analysis of the combined male and female data with a linear model, the best-fitting of 6 models examined, p = 0.99)
Study continuity	6 hours per day, 5 days per week
Study duration	24 months
Average experimental exposure	0.046 mg/m^3 for BMC_{05} group (0.25 x 6/24 x 5/7)
Human equivalent concentration	0.020 mg/m^3 for BMC_{05} group (particle with extrathoracic respiratory effects, RDDR = 0.453, based on MMAD = 0.68 µm and sigma g = 2.93)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference concentration	0.7 µg/m^3

The data of Reuzel *et al*. (1990, 1994) were examined with six quantal dose-response models (linear, log-normal, Weibull, logistic, quadratic, gamma) using USEPA BMDS 1.2. All models except the quadratic gave a good fit to the combined male and female data set. The linear model was selected as the best-fitting model. Possible differences between male and female susceptibility are suggested by the gender-specific data, although the significance of these differences is uncertain.

USEPA used the same two studies and a BMC_{10} approach to develop an RfC of 0.6 µg/m^3. Since USEPA used a 3-fold database uncertainty factor, their BMC_{10}-based RfC is comparable to the BMC_{05}-based OEHHA REL.

VII. Data Strengths and Limitations for Development of the REL

Strengths of the REL for MDI include the use of a well-conducted, long-term inhalation study, the observation of a NOAEL, and the estimation of a benchmark concentration. A limitation of the REL is that it is based on data on exposures to MDI "polymer" which actually contains nearly 50% monomer. Monomers may in some cases be more toxic than polymers. Thus, effects of pure monomeric MDI may occur at concentrations somewhat lower than observed in the reported study on MDI polymer. However, the capacity of MDI polymer to induce immunologic sensitization is greater than that of MDI monomer (Aul *et al*., 1999). The relative potential of MDI monomer and polymer to induce hyperplasia of the olfactory epithelium is unknown.

VIII. References

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